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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
34157-707.831

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on January 7, 2008

Signature Christine Nagy

Typed or printed name Christine Nagy

Application Number	Filed
10/530,164	April 4, 2005
First Named Inventor	
Susanne Binder	
Art Unit	**Examiner**
1651	Kim, Taeyoon

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96)

☒ attorney of agent of record.
Registration number 47,664.

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Registration number if acting under 37 CFR 1.34 _____

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January 7, 2008
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of 1 forms are submitted.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PRE-APPEAL BRIEF REQUEST FOR REVIEW

The rejections posited by the Office in the instant Application are based on clearly erroneous assumptions, and as a result, the Office's rejections are also in clear error. In contrast to the Office's position: (1) the term "confluent" is not new matter because the specification provides abundant support for confluent cultures; (2) the term "confluent" refers to cells that are in contact over the entire growth surface, and this is not taught by Dutt, which is limited to sparsely-distributed cultures on an amniotic membrane; and (3) the amniotic membrane of Dutt is not an equivalent to the collagen substrate of Liu because Dutt concluded that amniotic membrane inhibited cell growth while collagen promoted higher cell densities. As a result, Applicant respectfully requests allowance of the pending claims.

BACKGROUND

From the first Office Action, the Office has presented the position that the pending claims are obvious over Liu in view of Dutt. The Office argued that a skilled artisan would have been motivated to replace the collagen substrate of Liu with the amniotic membrane of Dutt because both substrates are considered art-recognized equivalents for growing RPE cells for transplantation.

In order to reach agreement with the Office, the pending claims of the instant Application were amended to require confluent retinal pigment epithelial (RPE) cells or confluent RPE equivalent cells on an amniotic membrane. Applicant provided clear support for "confluent" RPE and RPE equivalent cells in the specification, and argued that because the amniotic membrane of Dutt inhibited cell growth, Dutt would not be able to resolve the deficiencies of Liu to achieve the confluency required by the claims.

In the Advisory Action, the Office acknowledged that Dutt disclosed that amniotic membrane inhibited cell growth. However, the Office posited that the term "confluent" did not have support in the specification and was thus new matter. Further, the Office defined "confluent" to include sparsely-distributed cultures, and concluded that Dutt's cultures grown on amniotic membrane were confluent. Finally, the Office posited that because Dutt taught that both collagen and amniotic membrane inhibited cell growth, the two were suitable alternatives to each other.

For the reasons stated herein, the Office's positions are clearly erroneous and the pending claims patentable.

ARGUMENT

I. Office's Position That The Term "Confluent" Is New Matter Is Clearly Erroneous

The claims of the instant Application require confluent RPE cells or confluent RPE equivalent cells on an amniotic membrane. *See* Response of 11/28/2007, page 2, claim 42. Applicant provided support in the specification for the use of "confluent" cells. *Id.* at 5. However, the Office stated that the amendment introduced new matter into the application because the term "confluent" in claim 42 did not have appropriate support from the specification, finding "no disclosure of RPE cells grown on amniotic membrane until they become 'confluent' or a composite comprising 'confluent' RPE cells on the membrane." Advisory Action, page 2, first paragraph.

The Office is in clear error that the specification does not support confluent RPE cells on amniotic membrane. The instant Application provides abundant support that the composite comprises confluent cells and that claim 42 does not provide new matter:

Support in Specification	Paragraph
"[T]he step of culturing the retinal pigment epithelial cell or retinal pigment epithelial equivalent cell on the membrane is continued until the **cells reach confluence**."	¶ [0074]
"When RPE cells on each of the above **culture reached confluence**, the Ca^{2+} concentration in the culture medium was changed..."	¶ [0098]
"Each culture was followed with observation under a phase contrast microscope at 36 h after plating, at **confluence**..."	¶ [0099]
"**Confluence** [of rabbit RPE cells] was reached in about 7-9 days on dAM [denuded amniotic membrane]..."	¶ [0100]
"When **RPE cells reached confluence** on dAM [denuded amniotic membrane], the medium was switched to high Ca^{2+} DMEM/F12."	¶ [0101]

Further, the Office is in clear error in citing to paragraph [0066] of the Application as support that "RPE cells appear to be removed when they are subconfluent." Advisory Action, page 2, first paragraph. Paragraph [0066] provides no such support. Paragraph [0066] is directed to harvesting RPE cells from a retina using a cannula, which is a completely separate step from culture of RPE cells on amniotic membrane. Thus, paragraph [0066] does not negate the abundant support in the specification for confluent cultures of RPE or RPE equivalent cells on an amniotic membrane. In sum, the Office is clearly erroneous in concluding that the term "confluent" introduced new matter into the application.

II. Office's Definition of "Confluent" Culture Is Clearly Erroneous

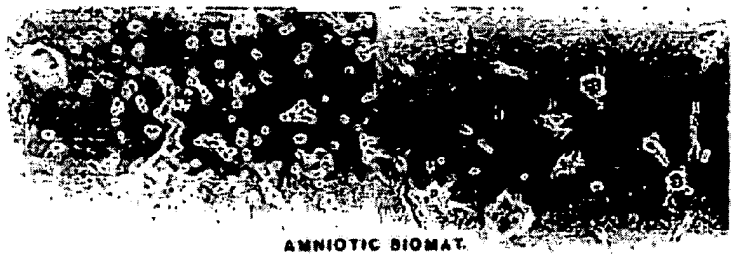
As enumerated above, the pending claims require a "confluent" culture of RPE or RPE equivalent cells. A confluent cell culture, as used in the art, is one in which the cells are in contact over the entire growth surface of the culture vessel. *See, e.g.*, Harrison & Rae, *General Techniques of Cell Culture* (1997), page 69 (confluent when "cells are touching each other and there is no more substrate space"); Pollard & Walker, *Basic Cell Culture Protocols* (1997), page 17 (confluent when the "culture surface is completely covered with cells"). Further, this definition of "confluent" is also contemplated by the Application. *See* Response of 11/29/07, page 5 (citing paragraph [0074] which states "about 16,000 to about 20,000 cells with high vitality are needed to cover a 4 mm^2 defect").

However, without citing any support, the Office posited that the term "confluent" means "the state of cells being adjoining/contacting." Advisory Action, page 2, first paragraph. The Office's definition of "confluent" is clearly erroneous and does not comport with the general understanding in the art. The Office's definition does not require that the cells be adjoining or contacting over the growth surface– the essence of a confluent culture. In fact, the Office's definition includes cultures that are not confluent, such as subconfluent cultures, turning the definition on its head. As a result, the Office's definition of "confluent" is clearly erroneous.

III. Office's Conclusion That Dutt Shows "Confluent" RPE Cells on Amniotic Membrane Substrate is Clearly Erroneous

Because the Office's definition of "confluent" is clearly erroneous, the Office incorrectly concluded that Dutt shows or suggests confluence of RPE cells on amniotic membrane based on an image in Dutt of some RPE cells in contact with each other on an amniotic membrane. *See* Advisory Action, page 2, first paragraph.

As explained above, a confluent culture requires that the cells not only be adjoining or contacting each other, but that the cells also cover the growth surface. Applicant stated that Dutt did not demonstrate such confluency of RPE cells on amniotic membrane. Response of 11/29/07 at page 6. Dutt plainly shows that at 24 hours (left panel) and at 96 hours (right panel), the RPE cells are sparsely distributed with large cell-free areas on the culture surface:



Dutt, page 1093, Fig. 2. By no stretch of the imagination should these cultures be considered confluent. Therefore, the Office is clearly erroneous that Dutt demonstrates a confluent culture of RPE cells on an amniotic membrane substrate, or even suggests that a confluent culture is possible on this substrate. *See* Response of 11/29/07 at page 6.

IV. Office's Conclusion That Amniotic Membrane Is An Art-Accepted Equivalent to Collagen Is Clearly Erroneous

In the Final Office Action, the Office posited that a skilled artisan would have been motivated to replace the collagen substrate of Liu with the amniotic membrane of Dutt, since both substrates are art-recognized equivalents for growing RPE cells for transplantation. Final Office Action, page 5. Applicant responded that the amniotic membrane of Dutt was not an equivalent to the collagen substrate of Liu because Dutt taught the growth inhibitory effects of amniotic membrane. Response of 11/29/07 at page 6. In light of this teaching, the Office's conclusion that a person of ordinary skill in the art would recognize the amniotic membrane of Dutt as an art-recognized equivalent to the collagen substrate of Liu is clearly erroneous.

The Office considered the collagen substrate of Liu and the amniotic membrane of Dutt to be equivalents because Dutt showed collagen and amniotic membrane as "tested substrates for RPE cells" and that "these substrates can be used for growth of RPE cells although they have different growth rate [sic]." Advisory Action, page 2, second paragraph. This logic does not pass muster. The Office erroneously equates the substrates merely because Dutt tested both as substrates for RPE cells, even though the Office acknowledged that collagen and amniotic membrane have different growth rates. Substrates with different growth rates cannot be considered equivalents merely because they were both tested.[1]

[1] Similarly, a voter would not consider two candidates running for president as equivalents merely because they were both running for the same position.

The Office offered an additional basis for the supposed-equivalence of amniotic membrane and collagen, positing that collagen and amniotic membrane are equivalent because "Dutt et al. disclose that collagen substrate also inhibits cell growth." *Id.*, citing Dutt at 1098. However, the Office's assertion is factually incorrect: the citation from Dutt does not support the equivalence of collagen and amniotic membrane. Rather, Dutt refers to a greater inhibition of cell growth by collagen polymerized floating gels as compared to collagen polymerized stationary gels. Dutt at 1098.

Indeed, contrary to the Office's statements, Dutt found that collagen and amniotic membrane were not equivalents, observing "dramatic differences" in the growth kinetics of collagen versus other substrates, including amniotic membrane. Dutt at 1098. Dutt concluded that "collagen IV promoted higher cell densities... **In contrast**, biomatrices prepared from placental and amniotic membranes were not as conducive to cell proliferation." *Id.* at 1093. Dutt further highlighted the differences between collagen and amniotic membrane substrates throughout:

Collagen Substrate	Amniotic Membrane Substrate
"Collagen IV **promotes higher cell density**" (p. 1098, 1093)	"[B]iomatrices prepared from placental and amniotic membranes were **not as conducive to cell proliferation**" (p. 1093)
"Collagen IV is also the most effective substrate in terms of **promoting higher cell density**" (p. 1099)	"The **growth inhibitory effects** of... amniotic membrane... were quite evident (Fig. 1, Table 2)." (p. 1093)
"We conclude in this report that collagen IV and ECM are the **best substrates** for enhanced expression of epithelial morphology in established HRPE cell lines." (p. 1099)	"Biomatrices prepared from amniotic and placental membranes **inhibited cell growth**." (p. 1098-99)

Therefore the Office is factually erroneous in the premise that Dutt showed that collagen inhibits cell growth and in its conclusion that collagen and amniotic membrane are equivalents. Clearly, Dutt found that collagen promoted higher cell density and was superior to the other substrates for growing RPE cells. Even if we accept the Office's clearly erroneous factual premise that Dutt discloses that collagen substrate inhibits cell growth, then one of skill in the art would not turn to Dutt in the first place[2] because Liu requires that the RPE cells be "apposed to a substrate to which they will attach and grow, and which is capable of being maintained in culture conditions appropriate for efficient growth of RPE cells." Response of 11/29/07 at page 6. Therefore, because the amniotic membrane of Dutt is demonstrably an unsuitable alternative to the collagen substrate of Liu, one of skill in the art would have no reason to turn to Dutt to achieve the cell growth necessary to achieve confluence of RPE or RPE equivalent cells on the amniotic membrane as required by Claim 42. *Id.*

[2] Furthermore, Dutt only describe the culture of a particular immortalized cell line, 0041, which differs from other types of RPE and RPE equivalent cells and is not even a cell type that is contemplated by the instant Application. Response of 8/28/07 at page 7. Dutt provides no indication that non-immortalized RPE cells could be cultured on amniotic membrane. *Id.* Applicant reserves the right to advance this argument in later briefing.

CONCLUSION

Applicant believes that this request fully complies with the submission requirements promulgated by the Patent and Trademark Office for a request for pre-appeal brief review. Applicant submits that the Office's rejections were based upon the legal and factual errors noted, and that correction of these errors will place the Application in a condition for allowance. Applicant respectfully requests a review of the matters identified in this paper.

Should any questions arise, any reviewing panel member is encouraged to contact the undersigned attorney at (858) 350-2306. The Commissioner is authorized to charge any additional fees that may be required, including petition fees and extension of time fees, or credit any overpayment to Deposit Account No. 23-2415 (Docket No. 34157-707.831).

Respectfully submitted,

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